Couple Based Approach for Assessing Environmental Pollutants and Human Reproduction and Development: Recent Findings from the LIFE Study

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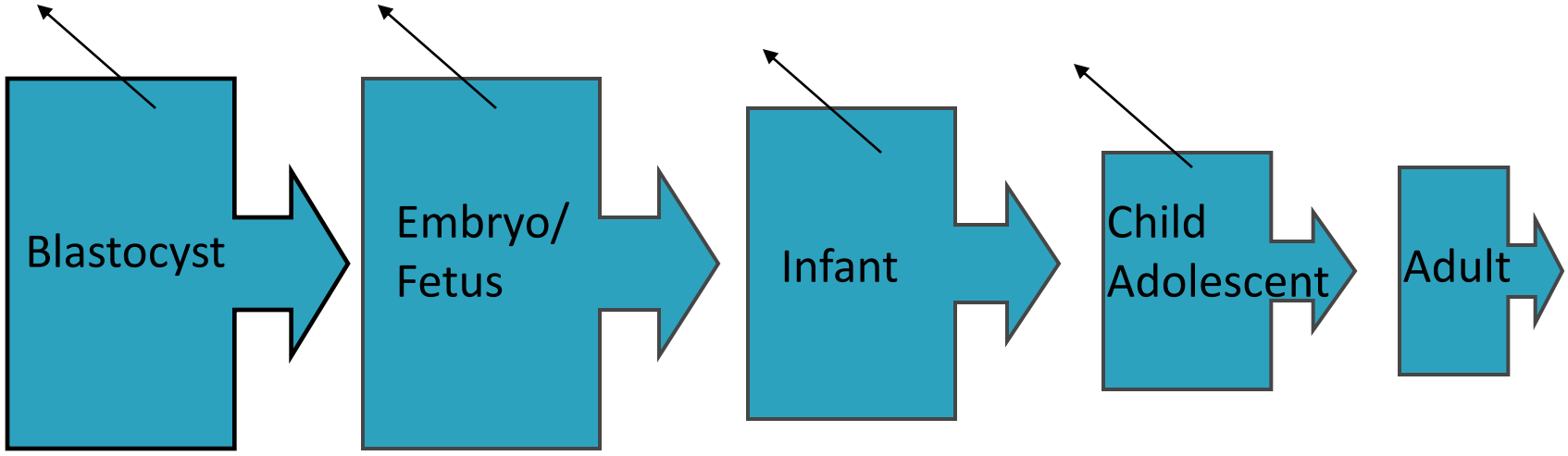
Developmental Origins of Health & Disease



Periconception Prenatal Postnatal Childhood

Paternal & Maternal Exposures

Life Course Epidemiology

Is Human Fecundity Declining?

- Males
  - Declining 2° sex ratios
  - Earlier pubertal onset
  - Declining semen quality
  - Increasing GU malformations
  - Increasing testes cancer

TDS (Skakkebaek et al. 2001)

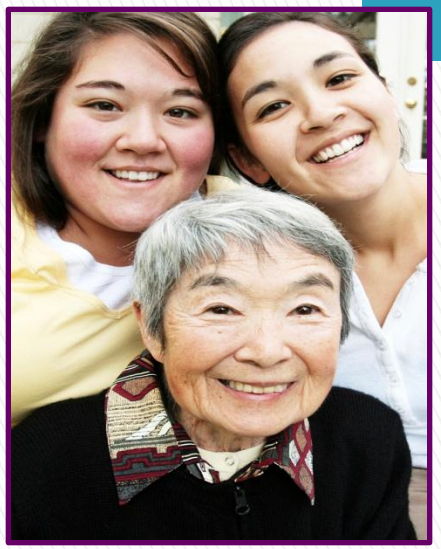
- Females
  - Earlier pubertal onset
  - Earlier onset gynecologic disorders
  - Declining fecundity (>TTP)
  - Declining fertility

ODS (Buck Louis et al. 2010)

"Across the developed world, birth rates are plummeting … social phenomenon, or is our biological fertility also declining? We don't yet know…"
Nature 2004

Environmental Influences on Reproduction & development Across the Lifespan

- Fecundity (biologic capacity)
  - Couple TTP
  - Pregnancy loss
  - Conception delay & infertility
  - Gestation
- Fertility (live births)
  - Live birth (multiples)
  - Birth size
  - 2° sex ratios



Reproductive Health

Children's Health

Women's Health

Study Sections & Urban Legends

- Prospective cohort designs with longitudinal data collection & biospecimens not feasible
  - Hard to recruit & retain women (couples even harder)
  - Too much participant burden
- Selection bias
  - Women will have healthier lifestyles
  - Women with fertility problems will be disproportionately represented
  - Women will minimize time already trying
- Men will not participate
  - Men will not keep daily diaries
  - Men will not provide necessary semen samples
- Home pregnancy kits will miss pregnancies

Conceptual & Methodologic Challenges Underlying Human Reproduction & Development

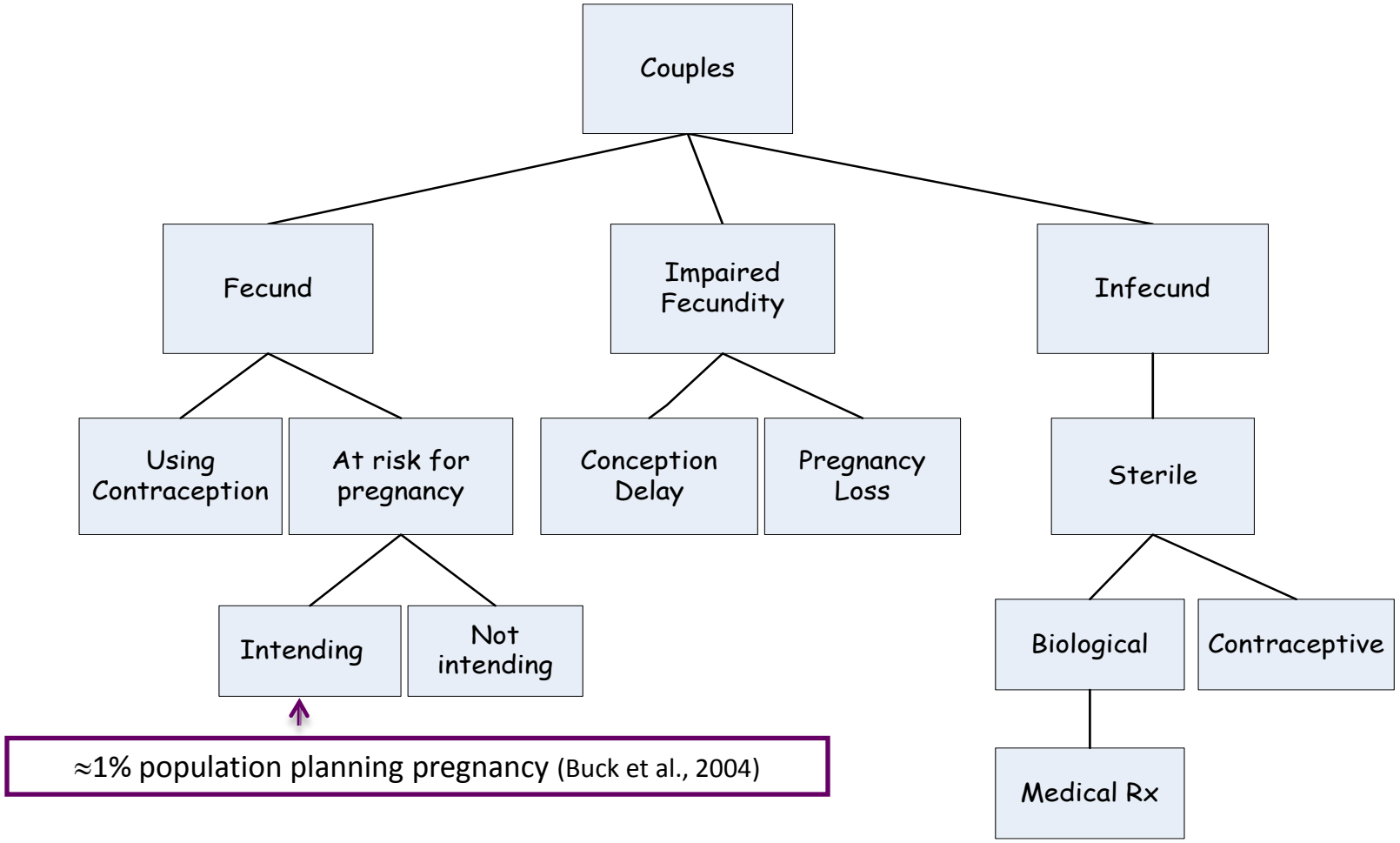
- Conceptual
  - Series of timed, highly interrelated & conditional outcomes
  - Some outcomes are “hidden”
  - Defining referent & study populations for couples planning pregnancy
- Methodologic – specifying the etiologic model
  - Endogenous & exogenous nature of reproductive factors
  - Hierarchical data structure
  - Correlated outcomes
  - Multiple exposomes
  - Conditioning on intermediates
  - Missingness & censoring

Trans-disciplinary teams needed for discovery, translation & improving population health…

Longitudinal Investigation of Fertility & the Environment – the LIFE Study

- Do persistent environmental chemicals affect human reproduction & development in the context of couples' lifestyles?
  - Study outcomes
    - 1° Time-to-pregnancy; infertility; pregnancy loss, gestation & birth size
    - 2° Menses; ovulation; reproductive profiles; semen quality; sex ratios
  - Chemicals
    - Completed - OCPs, PBDEs, PCBs, PFCs, metal, ctinine, phytoestrogens
    - Ongoing - BPA, phthalates, UV filters
  - Lifestyle
    - Alcohol, caffeine, exercise, fish consumption, smoking, stress, vitamins

Population Sampling

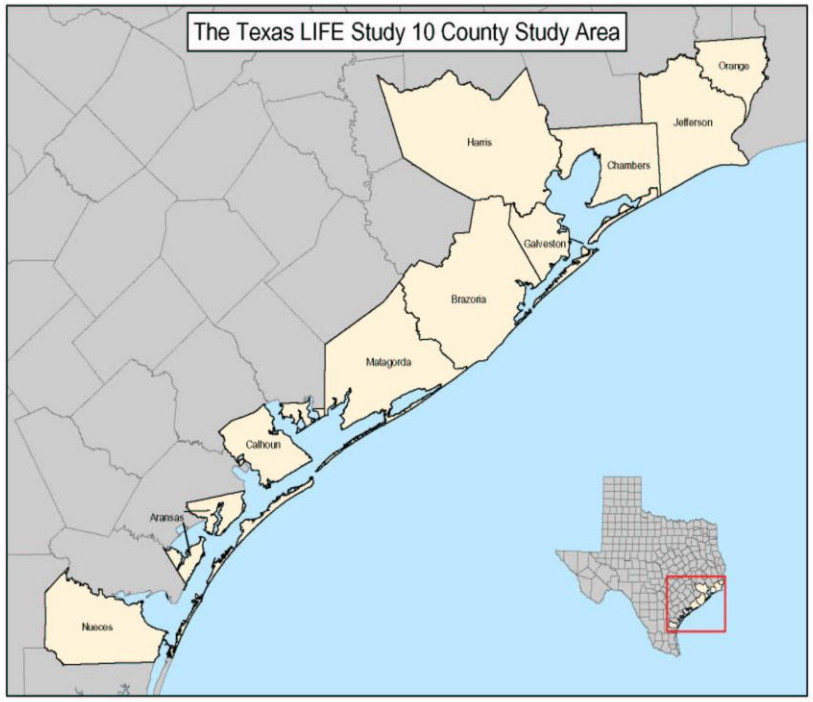


Recruitment Strategy – LIFE Study

Research Site	Michigan	Texas
Referent population	4 counties	12 counties
Sampling framework	InfoUSA®	Texas Parks & Wildlife Registry
Direct contact	Mailing with telephone follow up	Mailing with telephone follow up

Each partner must be contacted separately!

Maps


The Texas LIFE Study 10 County Study Area
Orange
Jefferson
Harris
Chambers
Galveston
Brazoria
Matagorda
Calhoun
Aransas
Nueces


LIFE Study Sites in Michigan
Lake Michigan
Lake Huron
Michigan
Ingham
Kalamazoo
Calhoun
Berrien
Lake Erie

Inclusion Criteria - Couples

- Ages 18-44 years; males aged >18 years
- Able to communicate in English/Spanish
- In committed relationship
- Wishes to conceive in next 6 months
- Planning to stop contraception to become pregnant

Retention Considerations

- Sensitive data collection
- Burden & remuneration
  - Estimating “reproducible” burden
  - $25 blood; $5 urine; $20 saliva; $20 semen
- Data collection options
  - Web based, hardcopy or both
- Supporting web based & hardcopy daily journals
- Iatrogenic harm
  - TTP induced stress
  - Couple differences in journal reporting

Delineating the Exposome

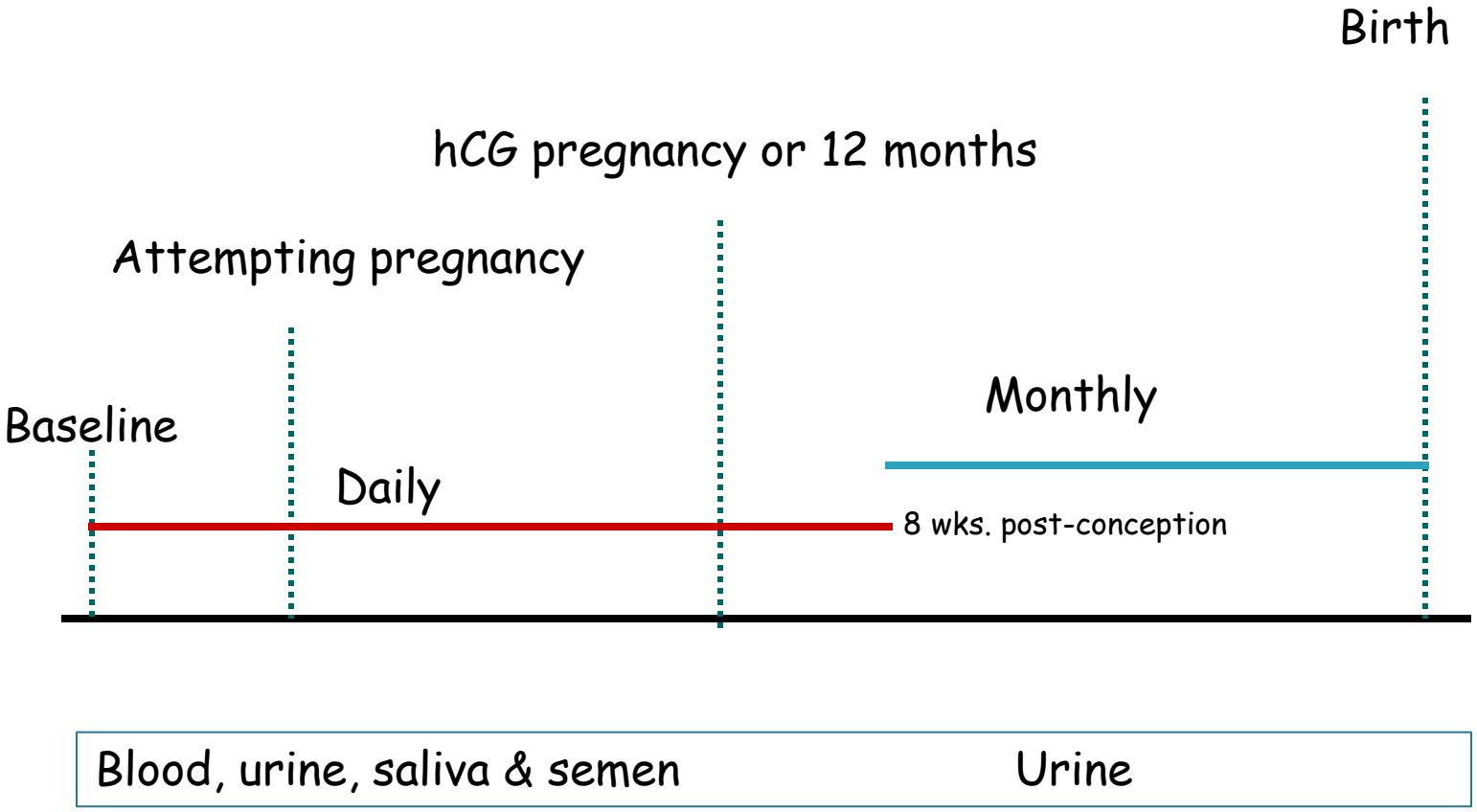
- Male
- Female
- Couple
- Conceptus, embryo, fetus

High dimensional longitudinal mixtures…
(Louis et al., 2011)

…totality of environmental exposures from conception onwards (Wild 2005)

… getting snapshots during critical windows of exposure (Rappaport & Smith 2010)

Time-Based Data Collection

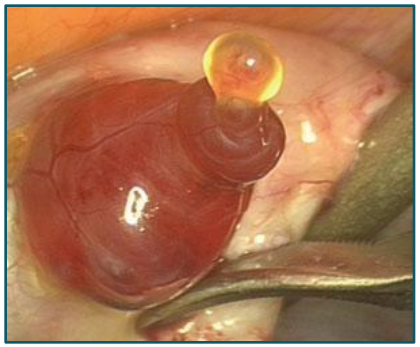


Home-Based Data Collection

Daily Journals

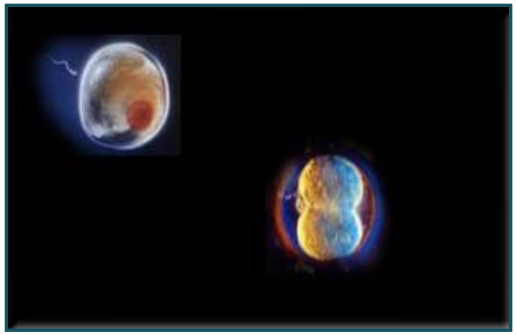
Home as Laboratory

Unobservable Outcomes



Ovulation

Fertilization



Cell Division

Home Biospecimen Collection & Testing- FEMALES

INITIAL DISPLAY

PRESS M BUTTON AND HOLD FOR
5 SECONDS UNTIL '1' APPEARS

DISPLAY AFTER 'M' BUTTON IS PRESSED

FERTILITY STATUS BAR

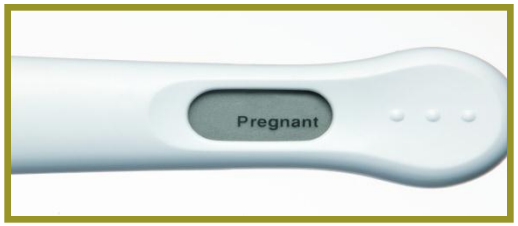
DISPLAY INDICATES THAT THE MONITOR
REQUIRES A TEST

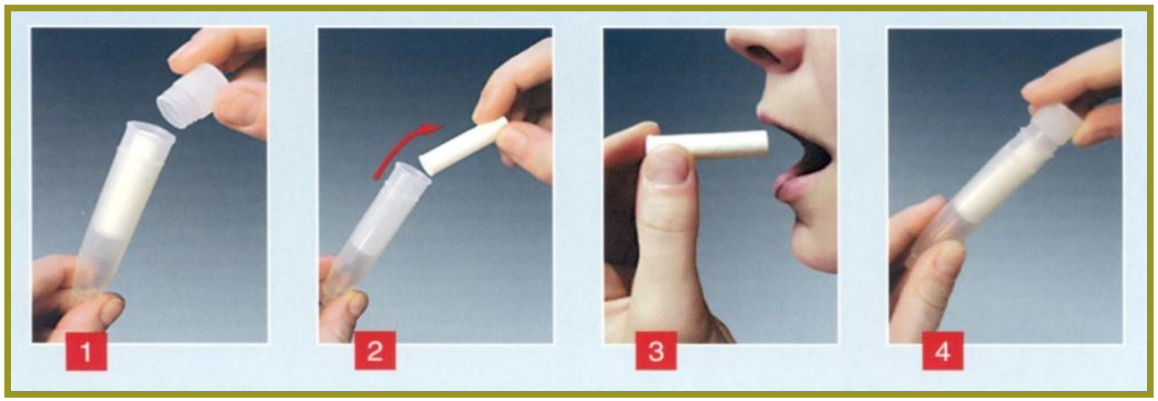
LOW FERTILITY:
very small chance of conception

HIGH FERTILITY:
increased chance of conception

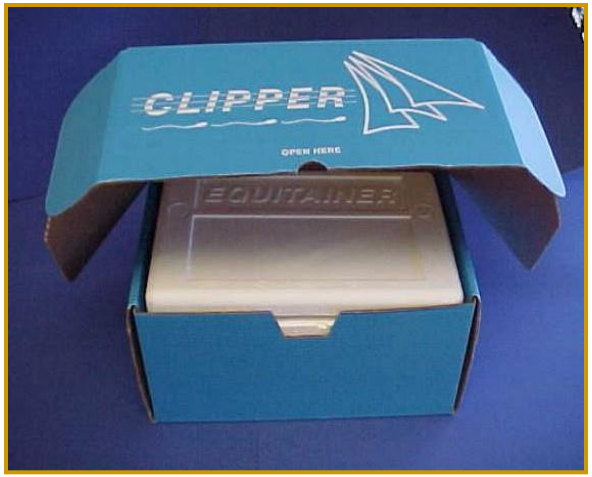
PEAK FERTILITY:
highest chance of conception

Home Biospecimen Collection & Testing- FEMALES cont'd





Home Biospecimen Collection-MALES



Emerging Results- LIFE Study

Recruitment

42% eligible couples enrolled

0.1% recruitment yield

	Letters Mailed (N)	Recruited* n (%)	Enrolled n (%)
Texas A&M (12 counties)	355,087	981 (3%)	397 (40%)
RTI (4 counties)	69,336	203 (1%)	104 (51%)

≈84% couples not screened

36% refused screening

Buck Louis et al., 2011

Sampling Frameworks – LIFE Study

- Few differences by sampling framework or by completion status
  - No difference by partners' ages, education, health insurance, or women's gravidity, parity
  - Couples completing study were more likely to be white & have higher household incomes than couples withdrawing

% Journal Cards Received

Card	Male	Female
Michigan		
•Journal	82	84
•Early pregnancy (daily)	--	80
•Pregnancy (monthly)	--	76
Texas		
•Journal	85	88
•Early pregnancy	--	82
•Pregnancy	--	81

Biospecimen Collection

Biospecimen	First Sample % Obtained	Second Sample % Obtained
Blood	100	--
Urine (6 mo. & pregnancy)	100	94 (77 & 95)
Saliva	98	87
Semen	94	77

Field Lessons to Date

- Challenging, targeting couples planning pregnancy within two months for population based recruitment
  - <1% couples planning pregnancy within two months
  - Some women already pregnant
  - Pregnancy intentions change
- Few language based barriers during telephone contact
- Drop out tend to be early
- Few couples consistently used web for data collection

Emerging environmental results…

Metals & Fecundability Odds Ratios

Adjusted Model	Female FOR (95% CI)	Male FOR (95% CI)
Cadmium (ug/L)	**0.77 (0.62, 0.97)**	0.85 (0.71, 1.01)
Lead (ug/dL)	0.97 (0.85, 1.11)	**0.85 (0.73, 0.99)**
Mercury (ug/L)	0.99 (0.87, 1.12)	0.98 (0.86, 1.11)
Cotinine (ng/ml)	0.98 (0.81, 1.18)	0.96 (0.83, 1.10)
Serum lipids (ng/g)	0.93 (0.82, 1.06)	0.98 (0.87, 1.10)
Age (years)	**0.80 (0.70, 0.91)**	**0.85 (0.75, 0.97)**
BMI (kg/m^2)	0.91 (0.79, 1.04)	0.99 (0.88, 1.12)
Site (Michigan/Texas)	1.23 (0.91, 1.66)	1.30 (0.96, 1.76)
Parity (null/parous)	**1.72 (1.34, 2.21)**	**1.66 (1.31, 2.11)**

Couples' Metal Exposures & Fecundability Odds Ratios

Adjusted Model*	FOR (95% CI)*
Female cadmium (ug/L)	0.81 (0.64, 1.02)
Female lead (ug/dL)	1.05 (0.91, 1.23)
Female mercury (ug/L)	1.00 (0.86, 1.16)
Male cadmium (ug/L)	0.93 (0.78, 1.12)
Male lead (ug/dL)	**0.83 (0.70, 0.98)**
Male mercury (ug/L)	0.98 (0.84, 1.14)
Female age	**0.81 (0.70, 0.94)**

*Adjusted for couples' cotinine, lipids, BMIs, female age (years) & difference between couples ages

Summary

- Feasibility of population based sampling
  - <1% of targeted samples planning pregnancy
  - 42% of recruited couples enrolled in study
  - 69% of enrolled couples completed study (drops out tend to be early)
  - Men did as well as women with study protocol
- Emerging environmental signals
  - Magnitude comparable to age & other lifestyle factors
  - Various classes of persistent compounds associated with reduced couple fecundity

Conclusions & Future Directions

- Emerging evidence supportive of a relation between environmental factors & couples fecundity
  - Effect comparable in magnitude to age & lifestyle
  - Is effect mediated through anovulation, altered menses or semen quality?
  - What are the implications for other fertility outcomes?
- Concerted efforts to define the exposome for both partners of the couple to delineate underlying mechanisms
- Implications for child health remain to be established

Males matter!

LIFE Study – Research Team

- NICHD
  - Drs. Zhen Chen, Sungduk Kim, Enrique Schisterman & Rajeshwari Sundaram
- Texas A & M University
  - Drs. Anne Sweeney
- RTI International
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- The EMMES Corporation
  - Dr. Rob Gore-Langton
- Ohio State College of Medicine
  - Dr. Courtney Lynch
- Emory University
  - Dr. Dana Boyd Barr
- CDC
  - Drs. Antonia Calafat, Steven Schrader, Andreas Sjödin